IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOVAIL LABORATORIES INTERNATIONAL SRL a corporation of Barbados,	)	
Plaintiff,	)	C.A. No. 05-586-GMS
	)	C.A. No. 05-730-GMS
v.	)	C.A. No. 06-620-GMS
	)	CONSOLIDATED
ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION	)	
Defendants.	)	

DEFENDANTS' OPENING BRIEF ON CLAIM CONSTRUCTION

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

CASES

Defendants Andrx Pharmaceuticals, LLC and Andrx Corporation (collectively, "Andrx") submit this memorandum in support of its proposed construction of disputed claim terms in U.S. Patent Nos. 5,529,791 ("the '791 patent") and 7,108,866 ("the '866 patent"), and in opposition to the constructions proposed by plaintiff Biovail Laboratories International SRL ("Biovail") in the meet-and-confer process.

I. INTRODUCTION

By these consolidated Hatch-Waxman Act patent litigations, Biovail has succeeded in keeping its would-be generic competitor, Andrx, out of the market for nearly two years, by means of a staggered patent strategy – asserting the '791 patent in August, 2005, and asserting the '866 patent at the close of expert discovery on the '791 patent.

It is apparent that Biovail's assertion of the '791 patent was merely intended to buy time until the '866 patent issued. After all, Biovail already has litigated and twice lost the question of whether the diltiazem beads that comprise Andrx's product in this case infringe any claim of the '791 patent.

Now, on claim construction of the '791 patent the third time around, Biovail seeks to relitigate the district court's and the Federal Circuit's prior construction of those claim limitations that Andrx's diltiazem beads previously have been found not to meet.

Biovail's strategy with respect to the '866 patent is essentially to refuse to construe the claim terms that expressly refer to United States Pharmacopeia ("USP") and FDA testing standards (often quoted by the inventors in the specification). Biovail refuses to provide claim constructions sufficiently specific to allow Andrx (or the Court) to determine whether Biovail really has the evidence necessary to establish infringement.

In what follows, Andrx will demonstrate that the prior courts' determinations and the binding intrinsic evidence support Andrx's proposed constructions of the disputed terms. Sections II and III set forth the legal standards for claim construction and the person of ordinary skill in the art – areas of the law with which Andrx knows the Court to

be familiar. Andrx's application of this well-settled law to the facts in this case is in Section IV, which begins on page 4.

II. LEGAL STANDARDS OF CLAIM CONSTRUCTION

A. The Basic Principles of Claim Construction

Claim construction is a question of law to be resolved by the court. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 389-90 (1996). It is "the judicial statement of what is and is not covered by the technical terms and other words of the claims." *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001). In undertaking proper claim construction, the Court should first look at "the words of the claims themselves." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). As with the interpretation of statutes, the words of a claim "are generally given their ordinary and customary meaning", which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). In order to determine the true meaning of a claim term, a court examines intrinsic and extrinsic evidence.

B. Intrinsic Evidence

The claims themselves, the patent specification, and the prosecution history are commonly referred to as "intrinsic" sources of meaning. *See, e.g., Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006). Such intrinsic evidence "is the most significant source of the legally operative meaning of disputed claim language." *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1370 (Fed. Cir. 2005) (internal citation omitted). Accordingly, courts are instructed to rely only on such intrinsic evidence, when possible, to construe patent claims. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 987 (Fed. Cir. 1995) ("[I]t is from the public record that a court should seek in a patent infringement case to find the meaning of claim language."), *aff'd*, 517 U.S. 370 (1996).

The Supreme Court and the Federal Circuit have found the claim language itself to be "of primary importance in the effort to ascertain precisely what it is that is patented." *Phillips*, 415 F.3d at 1312 (quoting *Merrill v. Yeomans*, 94 U.S. 568, 570 (1876)). Because the claim language is particularly and carefully chosen by the patentee, such terms "carry a presumption that 'they mean what they say and have the ordinary meaning that would be attributed to those words by persons skilled in the relevant art.'" *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2004). Accordingly, "claim terms take on their ordinary and accustomed meanings unless the patentee demonstrated an intent to deviate from" such meaning. *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1324 (Fed. Cir. 2002).

The Federal Circuit has emphasized that the specification "is the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315. Although limitations from the specification generally should not be imported into the claims, "where the specification makes clear at various points that the claimed invention is narrower than the claim language might imply, it is entirely permissible and proper to limit the claims." *Alloc, Inc. v. ITC*, 342 F.3d 1361, 1370 (Fed. Cir. 2003). For example, where the specification reveals a "disclaimer, or disavowal, of claim scope by the inventor . . . [then] the inventor's intention, as expressed in the specification, is regarded as dispositive." *Phillips*, 415 F.3d at 1316.

C. Extrinsic Evidence

Although the claim language, specification, and prosecution history are the best sources of information about a claim term's meaning, they may prove insufficient in some cases to construe a claim term. Only then may a court consider so-called "extrinsic evidence" such as dictionaries, learned treatises, expert testimony, and inventor testimony in construing the term. *See, e.g., Phillips*, 415 F.3d at 1317 (explaining that extrinsic evidence is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language'"). In no case, however, may extrinsic evidence override the

meaning suggested by the intrinsic evidence. *See, e.g., Vitronics,* 90 F.3d at 1584 ("extrinsic evidence . . . may not be used to vary or contradict the claim language").

"[D]ictionaries and treatises can be useful in claim construction", particularly technical dictionaries, which may assist a court "'to better understand the underlying technology' and the way in which one of skill in the art might use the claim terms." *Phillips*, 415 F.3d at 1318.

III. THE LEVEL OF ORDINARY SKILL IN THE ART

Claims must be interpreted from the perspective of a person of ordinary skill in the art as of the effective filing date of the patent application. *See Phillips*, 415 F.3d at 1312-13. For the '791 patent, that date is no earlier than June 26, 1991. For the '866 patent, that date is no earlier than December 10, 1999.

For both of the patents-in-suit, Andrx submits that the person of ordinary skill in the art is a person having a Master's or Ph.D. degree in chemistry, chemical engineering, and/or pharmaceutical sciences and at least two (2) years of additional industrial or practical experience in the field of pre-formulation and formulation of solid oral dosage forms. With respect to the '791 patent, Biovail has proposed a person or ordinary skill in the art as having a Bachelor's degree in pharmaceutical sciences or an analogous field, such as chemistry, chemical engineering, or biology, and two years of industrial formulation experience.[1]

IV. ARGUMENT

A. CLAIM CONSTRUCTION ISSUES REGARDING THE '791 PATENT

Each of the disputed claim limitations relating to the '791 patent are found in claim 1. The entirety of the text of claim 1 is reproduced, below, for context.

[1] Biovail has not yet stated what level of ordinary skill it will assert with respect to the '866 patent.

> 1. An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient, each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant, and wherein the wetting agent is selected from the group consisting of sugars, C_{12} -C_{20} fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

(J.A. Tab 1, A7-8 at 8:59-9:13.)

1. The Term "Extended-Release Galenical Composition" In Claim 1 Should Be Construed To Refer To Compositions In Their Dry State.

Andrx's Construction	Biovail's Construction
A pharmaceutical composition as it is prepared in the dry state and before ingestion by a patient, that releases the active ingredient over an extended period of time.	A pharmaceutical composition that releases the active ingredient over an extended period of time

The sole construction issue with respect to this limitation[2] is whether the limitation refers to the composition in its dry, finished pharmaceutical form, or if it broadly includes the dosage form in its "wet" state following administration to a patient.

[2] While the limitation "extended-release galenical composition" only appears in the preamble of claim 1, it is well-settled that a claim preamble that is "necessary to give life, meaning and vitality should be construed as if in the balance of the claim." *Pitney*

a) The Intrinsic Evidence Supports Andrx's Construction That The Term Be Read To Refer To The Dry State.

Under Andrx's proposed construction, this limitation refers to the finished pharmaceutical form of the claimed composition in the dry state. This is the plain meaning of the term "galenical composition." Biovail, on the other hand, reads the term "galenical" to be nothing more than a euphemism for "pharmaceutical." Biovail's construction cannot be correct, however, because when the applicants for the '791 patent wanted to refer to a "pharmaceutical composition," they plainly knew how to do it. (Joint Appendix of Intrinsic and Extrinsic Evidence (hereinafter "J.A.")[3] Tab 1, A-4 at 1:11-14.) In the claims, however, the applicants chose not to use that language. Instead, they chose to use the term "galenical composition." A person of ordinary skill in the art would have been familiar with the term "galenical composition." By 1991, the term had been used in a number of patents to refer to compositions that were designed to be used in or on the body to achieve a pharmacological result.

However, as a matter of plain logic, once the galenical composition is ingested in the body, it can no longer be a galenical composition as required by the claim. The claims require that the galenical composition contain beads which are coated with a microporous membrane that includes a water-soluble or water-dispersible polymer or

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Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999). Where a claim, as occurs here, refers back to the preamble for antecedent basis, both the preamble and body together define the subject matter of the invention. *See Bell Commc'ns Research, Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995) ; *see also Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 16 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1990) (holding that "the cutting blade", which appeared in both the preamble and was referenced repeatedly in the body, is "necessary to give meaning" to the claim and "is integral to the claim itself"). Here, the claim affirmatively refers back to the preamble for antecedent bases by referring to "the composition" – a short-hand form for the "extended-release galenical composition" recited in the preamble. (J.A. Tab 1, A8 at 9:1.

[3] All references are to the "Joint Appendix of Intrinsic and Extrinsic Evidence" to be filed at the same time as the parties' answering briefs.

copolymer. (J.A. Tab 1, A-8 at 9:2-6.) When the composition is exposed to the water-based digestive fluids in the stomach or in the gastrointestinal tract, a water-soluble polymer in the membrane would dissolve, leaving the composition lacking a required element. Consequently, as a matter of plain language, the galenical composition cannot be read to reach the post-administration, "wet" state.

Similarly, claim 3 requires that the composition of claim 1 contain about 8% of the wetting agent by weight of the composition. (J.A. Tab 1, A-8 at 10:3-5.) This limitation similarly confirms that the galenical composition of claim 1 must be read to refer solely to the dry state. Once the composition enters the body, an unknown amount of gastric fluid would enter the composition, adding an unknown amount of weight to the composition. It would, therefore, be impossible to determine if the claimed composition contained the required "about 8%" by weight of the wetting agent post-ingestion. Claim 3 only makes sense if the composition is limited to the composition to the dry state, where a person of skill in the art could calculate the percentage of wetting agent in the composition by weight.

Moreover, counsel for Andrx has found no reference in which a solid oral dosage form "galenical composition" has included as an ingredient any type of gastric fluid or other bodily fluid. If, as Biovail asserts, the plain meaning of a "galenical composition" includes solid oral dosage forms wherein the composition includes gastric fluids, surely someone somewhere prior to the filing date of the application published a description of a galenical composition which expressly includes gastric fluids.

For each of these reasons, Andrx respectfully requests that the Court construe this limitation in accordance with Andrx's proposed construction.

2. The Term "Beads" Refers To The Dry, Uncoated Material That Is Coated With A Microporous Membrane.

Andrx's Construction	Biovail's Construction
This limitation refers to the dry, uncoated material that is subsequently coated with a microporous membrane to form the galenical composition referred to in the claim.	The structure wherein the wetting agent is in admixture with one or more diltiazem salts to maintain the solubility of the diltiazem when the composition is exposed to pH conditions of the gastrointestinal tract or other adverse conditions the composition will meet *in vivo*.

Like "extended-release galenical composition," the sole claim construction issue is whether the claim limitation "beads" refers to the dry, uncoated material that is subsequently coated to form the galenical composition required by the claim, as Andrx asserts, or whether the claim limitation can be read broadly to refer to any structure having a wetting agent and a diltiazem salt in admixture when wet.

a) The Intrinsic Evidence Supports Andrx's Proposed Construction That "Beads" Be Read To Refer Solely To The Dry State.

The '791 patent specification clearly states that "the present invention" is "constituted by beads containing [a diltiazem salt] associated with at least a wetting agent . . . ." (J.A. Tab 1, A-4 at 2:54-58.) Similarly, the '791 patent specification states that the "present invention relates also" to a "process entailing preparing beads and coating the same with a single microporous membrane." The specification describes methods to manufacture the beads, and states "[t]he obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed." (J.A. Tab 1, A-5 at 4:48-49.) According to the specification, the "microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads." (J.A. Tab 1, A-5 at 4:64-67.)

The specification also includes two specific examples for making the claimed beads. Examples 1 and 2 in the '791 patent specification discuss forming beads and drying the beads. Examples 3 and 4 relate to applying the microporous membrane to the dried beads from Examples 1 and 2, respectively, and, after another round of drying, the specification refers to the product of Examples 3 and 4 as "coated beads," not "beads." (J.A. Tab 1, A-6 at 6:29, 6:61.) Thus, the specification is absolutely clear that the term beads is used to refer to the dried material of diltiazem salt and wetting agent in dry admixture.

The '791 patent file history similarly supports Andrx's construction. During prosecution of the '791 patent, the applicants characterized their invention in the following manner:

> Thus, at the outset, it is noted that the present composition is characterized by the use of beads consisting essentially of in admixture together an effective amount of Diltiazem or one of more salts thereof as an active ingredient and the wetting agent as defined in the claim. The beads are also coated with a microporous membrane as defined in the claims.

(J.A. Tab 5, A-71 (emphasis in original.) In that same amendment, applicants distinguished a particular reference (the "Debregeas reference") by stating that the beads in the present invention could not be made according to the method of Debregeas. The Debregeas method entailed starting with a sugar core, and layering diltiazem on that core to form a bead.[4] (*Id.* at A-72.) The applicants further stated, "[c]learly, it is impossible to have a sugar central core in a homogenous bead as in the present invention. Such a bead is, by nature, heterogeneous." (*Id.* (emphasis in original).) Again, the applicants were clearly referring to the dried, uncoated beads, and stated that such a bead made from a central sugar core could in no way be homogeneous.

[4] Andrx's proposed product, like that described in Debregeas, starts with a central sugar core upon which diltiazem salt is deposited.

Now, however, despite the clear statements in the specification and file history as to "beads" referring to the dry state, Biovail seeks to broaden the scope of the '791 patent by pointing to statements in the file history that do not in any way alter the proper construction of the term "bead." For example, in distinguishing the Debregeas reference, the applicants stated as follows:

> The saccharose contained in the central core of the bead [in the Debregeas reference] cannot act as a wetting agent because in order to do so the saccharose must be mixed with the Diltiazem and, therefore, saccharose must be in solution with Diltiazem. Unfortunately, in this system [the system disclosed in the Debregeas reference] saccharose can only end up in solution after all the layers of Diltiazem are dissolved. In other words, saccharose can only become effective when there is not [sic] longer a need therefor.

(J.A. Tab 2, A-21 (emphasis in original).) First, this statement does not use the term "bead" in connection with the post-ingestion "wet" state. The applicants carefully did not use the term "bead" to refer to anything other than the bead in the dry state. In the quoted passage, the applicants further discuss how an admixture could ***never*** occur in the Debregeas system (even if wet), but do not use the term "bead" when discussing this hypothetical situation. In fact, this passage makes clear that the prior art Debregeas approach (which Andrx employs in formulating its proposed product in that diltiazem is deposited onto a central sugar core) cannot contain an admixture even when wet. Curiously, Biovail is relying on a passage distinguishing prior art (that Andrx practices) to support a claim construction argument that they contend would cover that very same prior art process.

For these reasons, Andrx respectfully requests that the Court construe the term "Bead" in accordance with Andrx's proposed construction.

3. The Term "Each Bead" Refers To Every Single Bead.

Andrx's Construction	Biovail's Construction
The "each bead" limitation requires that every single bead must contain diltiazem salt and wetting agent in admixture.	Refers to the beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient. This term does not require that every single bead of the composition contain diltiazem salt and wetting agent in admixture.

The sole claim construction issue here is whether the word "each" is used in its ordinary, customary meaning to refer to every single one. The word "each" should be construed to refer to every single bead in the claimed galenical composition. Biovail seeks to construe the word "each" as, essentially, "not each" or, most generously, "some." Applying any construction other than Andrx's proposed construction effectively reads the word "each" out of the claim language, which is improper. *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1157 (Fed. Cir. 1995) ("We must give meaning to all the words in Exxon's claims.").

a) The Intrinsic Evidence Confirms That "Each Bead" Must Be Read To Refer To Every Single Bead.

The '791 specification uses the term "each" in its customary sense to refer to "every single one." For example, referring to prior art diltiazem formulations, the specification states "after each administration . . . a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established." (J.A. Tab 1, A-4 at 1:39-43.) This statement simply cannot be read to refer to any fewer than every single administration and retain any meaning. Similarly, at column 7 of the '791 patent, the specification describes a testing protocol in which healthy subjects received in random order doses of "each of the 2 products," and at "each of the eight day [sic]" blood samples were drawn. (J.A. Tab 1, A-7 at 7:25-34.) Again, the specification is clearly using the word "each" in its customary manner to refer to every single one.

Moreover, the '791 patent specification is absolutely clear that "each bead" refers to every single bead. The specification teaches that the beads in the claimed composition must be uniform. (J.A. Tab 1, A-6 at 5:54-6:23.) The specification describes two different specific examples for forming "beads." In each of the two examples, the beads are formed by mixing various ingredients including a diltiazem salt and a wetting agent, and then made into spheres. In each of the two examples, the resulting "beads" are dried to remove any moisture, and then sifted or sieved to obtain beads with the appropriate desired dimensions. (*Id.*) The specification then describes adding a microporous membrane to the dried beads, and, after another round of drying, refers to the product as "coated beads." (*Id.*) Thus, the specification is clear that the dried beads in each example are made in the same manner.

During prosecution of the '791 patent, the applicants confirmed to the patent office that uniformity of the beads was critical to the invention. Applicants tendered a declaration of named-inventor Arthur Deboeck, who sought "to demonstrate that the 'center' or 'core' of the present invention is an inherently homogeneous or uniform composition. . . ." (J.A. Tab 3, A-28.) In his declaration, Deboeck described an experiment in which the beads of Example 2 in the '791 specification were prepared on 6 different occasions to determine the homogeneity of the beads. (*Id.* A-29.) Deboeck concluded that the beads were perfectly homogeneous in the six different trials. (*Id.* A-30.) He further stated "[t]his step was carefully evaluated, as can be seen by the amount of analysis performed, as it is ***essential*** to the performance of the final product that the components of the core be homogeneous." (*Id.* A-31 (emphasis added).)

Biovail offers nothing in support of its spurious proposed construction. Presumably, Biovail will seek to bootstrap its faulty construction by arguing that the claim uses the transitional word "comprising," which therefore makes the claim open-ended. However, even where claims use the open-ended transitional word, "comprising," claims containing the word "each" have been found to mean every single one.

In *ResQNet.com, Inc., v. Lansa, Inc.*, the Federal Circuit held that "each" in an open-ended "comprising" claim meant "each (and every)". 346 F.3d 1374, 1379 (Fed. Cir. 2003). The Federal Circuit held that the "language shows that the claimed algorithm evaluates attributes of each (and every) field in the information to be displayed." *Id.* at 1377,1379. District courts have also consistently held that "each" should be given its customary meaning of every single one. For example, in *Medtronic, Inc. v. Guidant Corp.*, the court held that "each" in an open-ended "comprising" claim means "every one of two or more considered individually or one by one," citing the Random House College Dictionary. *Medtronic, Inc. v. Guidant Corp.*, Nos. 00-1473, 00-2503, 2004 WL 1179338, at *42 (D.Minn. May 25, 2004) (emphasis added) (Ex. A hereto). Similarly, in *Genlyte Thomas Group LLC v. Lutron Elecs. Co.*, No. 3:02-CV-0602-K, 2004 WL 690847, *5 (N.D.Tex. Mar. 31, 2004) (Ex. B hereto), the court held that "each" means "every" when used as an adjective – as it is in claim 1 of the '791 patent claim. Finally, in *Synvasive Corp. v. Stryker Corp.*, the court looked to Webster's Dictionary in construing "each" to mean "all considered one by one". 425 F. Supp. 2d 1105, 1115-1116 (E.D.Cal. 2006). The claim recited "a surgical saw blade comprising . . . a centrally positioned long axis . . . wherein each hypotenuse is oriented at least one of towards and away from the centrally positioned long axis". *Id.* at 1110. The court held that "each" meant "all" of the individual hypotenuses were either positioned towards the axis, or all were oriented away from it. *Id.* at 1116. Consequently, even in open-ended "comprising" claims, the word each should be given its customary meaning of "every single one."

b) The Commonly Understood Meaning Of The Word "Each" As Shown By A Dictionary Entry Confirms The Correctness Of Andrx's Construction.

Finally, the word "each" is commonly defined as "***every one*** of two or more considered individually or one by one." (J.A. Tab 8, A-98 (emphasis added).) The

applicants have given no signal in the specification or throughout the file history that they intended to or did use the word "each" in any kind of alternative or specialized manner.

For these reasons, Andrx respectfully requests that the Court construe the "each bead" limitation in accordance with Andrx's proposed construction.

4. The Term "An Effective Amount Of Wetting Agent" Requires That The Wetting Agent Act Within Each Bead.

Andrx's Construction	Biovail's Construction
An effective amount of wetting agent means an amount of wetting agent that acts within each bead to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein as further required by the claim language.	An amount of wetting agent sufficient to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein

The sole claim construction issue with respect to this limitation is whether the claim requires that the action of the wetting agent occur within the bead. Under Biovail's proposed construction, the wetting agent need not actually act to maintain the solubility of diltiazem in each bead or ensure that the solubility of the diltiazem is unaffected by the pH of the gastrointestinal tract.

a) The File History Confirms That An Effective Amount Of Wetting Agent Must Act Within Each Bead.

Andrx's proposed construction is correct, because it mirrors what the applicants told the patent office in order to obtain issuance of the '791 patent over prior art: "In essence, in admixture, the wetting agent appears to control or strongly influence the solubility of Diltiazem and does not permit this solubility to be affected by pH or other adverse conditions in the gastrointestinal tract. ***Further this control appears to occur within the core of Diltiazem and wetting agent.***" (J.A. Tab 5, A-71.) Similarly, applicants clearly stated to the patent office that "[t]he wetting agents claimed in the

present invention are substances which are believed to modify the solubility of diltiazem ***inside the coated beads*** when they are placed in a dissolution medium or when they are ingested by a mammal." (J.A. Tab 5, A-77 (emphasis added).) Biovail's proposal merely parrots additional claim language, and provides no support for its proposed construction, ignoring these clear statements to distinguish prior art made under a duty of candor to the patent office.

Consequently, Andrx respectfully requests that the Court construe this limitation in accordance with Andrx's proposed construction.

5. The Term "Admixture" Requires That The Entirety Of The Bead Be Homogeneous.

Andrx's Construction	Biovail's Construction
Admixture means two or more items that are commingled and interdispersed to obtain a homogeneous product (in this case, bead). In addition, the claim language "each bead containing . . . wetting agent in admixture with the one or more diltiazem salts requires that the entirety of the bead be homogeneous. The term "homogeneous" means that samples taken anywhere within the bead have identical compositions. Admixture should be read to refer to the dried, uncoated bead that is subsequently coated with a microporous membrane and included in the galenical composition.	Means a homogeneous admixture of one or more diltiazem salts and wetting agent can be found at a point in time during the life of the compositions, in particular during their in vivo transit from the stomach to the less acidic environment of the intestinal tract. Thus, a formulation will satisfy the admixture language of the '791 patent claims if the formulation is exposed to pH conditions that are found in the gastrointestinal tract, and operates such that the beads of the formulation include a homogeneous admixture of one or more diltiazem salts and wetting agent in those conditions. The term homogeneous means having one or more salts of diltiazem and wetting agent throughout the admixture of one or more salts of diltiazem and wetting agent.

There are two claim construction issues as to this limitation. The first issue is whether the term "admixture" as used in the claim requires homogeneity throughout the bead. The second issue is whether the term "admixture" in the claim limitation "each bead containing one or more diltiazem salts and an effective amount of wetting agent in

admixture" refers to the dried bead, or whether it also refers to "wet," post-ingestion beads.

a) Prior Decisions Relating to the '791 Patent Require Adoption Of Andrx's Claim Construction.

This is not the first time that courts have construed this claim language. In *Biovail Corp. Int'l v. Andrx Pharms., Inc.*, 158 F.Supp.2d 1318 (S.D. Fl. 2000), *aff'd*, 239 F.3d 1297 (Fed. Cir. 2001) , Biovail failed to prove that Andrx's proposed generic form of Tiazac infringed the '791 patent. The district court construed "admixture" to mean "two or more items commingled and interdispersed to obtain a homogeneous product." *Biovail*, 158 F.Supp.2d at 1325. The term "homogeneous" was held to mean "that samples of the product taken anywhere throughout the product should have the same compositions." *Id.* The district court also held that "it is clear that the claims of the '791 patent require that the wetting agent and diltiazem be in admixture ***in the dry state***." *Id.* at 1329 (emphasis added). The district court held that Biovail was "estopped from asserting that the inert sugar core of the Andrx formulation is a 'wetting agent' within the scope of the claims of the '791 patent" "because Biovail continuously argued on numerous occasions that the use of a sugar core surrounded by a diltiazem layer to form a heterogeneous structure . . . was not within the scope of the claims of the '791 patent." *Id.* The district court also addressed Biovail's argument that the admixture could be formed in the wet state, and held that "Biovail's own tests, particularly the Electron Scanning Microscope (ESM) slides submitted in evidence do not show that a homogeneous admixture is formed in the Andrx product." *Id.*

On appeal, the Federal Circuit held that the district court construed the "admixture" limitation consistently with its construction. *Biovail*, 239 F.3d at 1303. Turning to the district court's determination that Andrx's proposed product did not infringe the '791 patent claims, even in the wet state, the Federal Circuit held that "even assuming *arguendo* that 'admixture' is not limited to dry state compositions and that

sugar as used in Andrx's product is a 'wetting agent,' the district court's determination that Andrx's product does not literally infringe claim 1 of the '791 patent was not clearly erroneous." *Id.* Thus, the Federal Circuit was quite skeptical that the claims of the '791 patent were not limited to the dry state, but because there was no error that Biovail's proffered evidence did not demonstrate the presence of an admixture in Andrx's proposed product even when wet, the Federal Circuit did not address that question.

Biovail now seeks yet another bite at the claim-construction apple, seeking to broaden the previously-established construction to allow the admixture to occur "at any point in time during the life of the composition," and seeking a peculiar type of homogeneity – homogeneity that does not require the same composition throughout a sample at all.

b) The Intrinsic Evidence Supports Andrx's Proposed Construction.

Just as the last time Andrx and Biovail litigated what these claims mean, Biovail is estopped from arguing that depositing diltiazem on a sugar sphere creates an admixture. *Biovail*, 158 F. Supp. 2d at 1329. The term "admixture" was added to the claims to distinguish over the Debregeas reference which described layering diltiazem onto a sugar sphere. *Biovail*, 239 F.3d at 1302. The applicants addressed the Debregeas reference at length during prosecution of the '791 patent.

> In fact, such a procedure is impossible as microgranules of the type constituted by a central core as in Debregeas et al cannot be produced by the extrusion-spheronization process. By contrast, in accordance with the present invention, the extrusion-spheronization process leads to homogeneous type beads while the "building-up" process, starting with a sugar core, leads to heterogeneous type beads. Clearly, it is impossible to have a sugar central core in a homogeneous bead as in the present invention. Such a bead is, by nature, heterogeneous.

(J.A. Tab 5, A-74.) Similarly, the applicants tendered a declaration of named-inventor Arthur Deboeck to the patent office for the purpose of demonstrating "that the 'center' or

'core' of the present pharmaceutical composition is an ***inherently homogeneous or uniform composition*** of Diltiazem or one or more salts thereof and wetting agent. . . ." (J.A. Tab 3, A-28.) Deboeck presented data from several experiments, and concluded that "the composition of the core is perfectly homogeneous." (*Id.* A-30.) Deboeck went on to state that "[t]his step was carefully evaluated, as it is ***essential*** to the performance of the final product that the components of the core be homogeneously mixed." (*Id.* A-30 – A-31 (emphasis added).)

Similarly, Biovail's identified support only serves to underscore that Andrx's proposed construction is correct. For example, Biovail cites to the following statement:

> By contrast, the present formulation contains Diltiazem or one or more salts thereof in admixture together with the wetting agent. By combining the wetting agent in admixture with Diltiazem or one or more salts thereof, the solubility of the Diltiazem may be controlled and rendered independent of pH. This is quite important due to the wide variation in pH in the gastrointestinal tract.

(J.A. Tab 5, A-72 (emphasis in original).) Based on the numerous representations distinguishing the prior art (sugar sphere), Biovail is estopped from asserting that the '791 patent claims cover Andrx's proposed product.

c) Biovail's Proposed Construction Is Incorrect In That It Appears To Allow For "Localized" Homogeneity.

Andrx's proposed construction requires that the entirety of the bead be homogeneous. This is the construction that was previously used, and affirmed by the Federal Circuit. Indeed, the full claim limitation in which the term "admixture" appears states: "each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts. . . ." (J.A. Tab 1, A-7 at 8:62-65.) Biovail, on the other hand, appears to construe the limitation as only requiring that the "beads include a homogeneous admixture," and that homogeneous "means having one or more salts of diltiazem and wetting agent throughout the

admixture." Consequently, under Biovail's claim construction, the bead need not be homogeneous. Indeed, it appears that under Biovail's construction "localized" pockets within a bead that contain a diltiazem salt and a wetting agent (even if in different amounts from location to location) would fall within Biovail's claim construction.

This is a peculiar interpretation of "homogeneous." First, as the district court construed homogeneous, homogeneity properly required that "samples of the product taken anywhere throughout the product should have the same compositions." *Biovail*, 158 F. Supp. 2d at 1325. The Federal Circuit held that the district court construed the "admixture" limitation consistently with its construction. *Biovail*, 239 F.3d at 1303. Under that construction, each location within a bead is required to be uniform in terms of chemical composition. That is what homogeneous means. For example, Webster's Encyclopedic Unabridged Dictionary of the English Language defines "homogeneous" as "composed of parts all of the same kind." (J.A. Tab 9, A-101.) Biovail seeks to pay lip service to the homogeneity requirement by construing the claim to only require that the bead "include" a homogeneous admixture, wherein homogeneous only requires the presence of "one or more salts of diltiazem and wetting agent throughout the admixture." Joint Claim Chart Ex. B (D.I. 142). Thus, in Biovail's view, homogeneity does not require that the composition present in a "homogeneous" region be the same from location to location. Rather, under the Biovail proposed construction, so long as some diltiazem salt is present somewhere in the vicinity of some other amount of wetting agent, that is a homogeneous admixture for purposes of the claim. Such a construction would essentially eliminate the admixture limitation from the '791 claims altogether.

For these reasons, Andrx respectfully requests that the Court construe the "admixture" limitation in accordance with Andrx's proposed construction.

6. The Term "To Maintain The Solubility Of The Diltiazem In Each Bead" Requires That The Wetting Agent Actually Acts Within Every Single Bead To Hold The Solubility Value Of Diltiazem Constant.

Andrx's Construction	Biovail's Construction
This limitation requires that the numerical value of the solubility of the free base diltiazem be maintained, i.e., be held constant, in every single bead. "Solubility" refers to the amount of material (expressed in units of mass) that are capable of being dissolved in a given amount of solvent to give a saturated solution (expressed in units of volume) at a given temperature.	Means the wetting agent does not permit the solubility of the diltiazem to be affected by the pH or other adverse conditions of the gastrointestinal in a manner that would prevent a gradual release of the drug in a relatively uniform manner. The term solubility means the condition of being soluble. The term "each bead" refers to the beads containing an effective amount of one or more of said diltiazem salts as the active ingredient.

The issues presented for the Court's decision relating to this limitation are (1) whether "solubility" means the commonly understood numerical value, or merely refers to the condition of being soluble; (2) whether "maintain" means to hold constant, or "not . . . prevent a gradual release of the drug in a uniform manner"; and (3) whether "each bead" refers to every single bead, or if it merely refers to "beads containing an effective amount of one or more of said diltiazem salts as the active ingredient."

a) "Solubility" Refers To The Amount Of A Substance That Dissolves In A Given Volume Of Solvent At a Given Temperature.

"Solubility" is a commonly used term in the art. It refers to a property of a chemical substance. A glossary from a 1990 introductory General Chemistry textbook sets forth the commonly understood technical definition of the term: "Solubility is the amount of a substance that dissolves in a given quantity of solvent (such as water) at a given temperature to give a saturated solution." (J.A. Tab 11, A-107.) Biovail argues that "solubility" refers merely to the "condition of being soluble."

The word "solubility" does not appear in the '791 specification (apart from its presence in the claims). During prosecution of the '791 patent, the applicants told the

patent office that the wetting agent controlled the solubility of diltiazem to render the solubility independent of pH.

> In essence, in admixture, the wetting agent appears to control, or strongly influence, the solubility of Diltiazem and does not permit this solubility to be affected by the pH or other adverse conditions in the gastrointestinal tract. Further, this control appears to occur within the core of diltiazem and wetting agent.
>
> * * *
>
> By combining the wetting agent in admixture with Diltiazem or one or more salts thereof, the solubility of the Diltiazem may be controlled and rendered independent of pH.

(J.A. Tab 5, A-71 – A-72.) Under Biovail's proposed construction, where solubility refers merely to the condition of being soluble, the file history statements relating to solubility control and pH independence would be meaningless – any material that is even slightly soluble in a given solvent would always be in the "condition of being soluble," whether in the presence of a wetting agent or not. Similarly, during prosecution, the applicants stated that "[t]he wetting agents claimed in the present invention are substances which are believed to ***modify the solubility*** of diltiazem inside the coated beads when they are placed in a dissolution medium or when they are ingested by a mammal." (J.A. Tab 5, A-77 (emphasis added).) Under Biovail's construction, the wetting agent would do nothing to modify whether the diltiazem was in a "condition of being soluble." Rather, the applicants were clearly referring to the wetting agent's action to control and modify the particular level (or value) of solubility to be independent of pH.

Even Biovail's cited support cannot be read to square with Biovail's definition of "solubility." Biovail cites to several passages from the file history in which the applicants told the patent office that "[t]he control affords a gradual release of Diltiazem in a relatively uniform manner over a period of about 24 hours." (J.A. Tab 4, A-51.) However, the control of solubility there refers to maintaining a constant value of

solubility such that the diltiazem is not highly soluble under one set of conditions and slightly soluble under another set of conditions. However, even in such a case – where the diltiazem was highly soluble under one set of conditions and only slightly soluble under another – Biovail's construction of "solubility" would include that case because in both sets of conditions the diltiazem would still be in a "condition of being soluble." Biovail's construction of "solubility" is, therefore, plainly incorrect.

For these reasons, Andrx respectfully requests that the Court construe "solubility" in accordance with Andrx's proposed construction.

b) "Maintain" Refers To Holding The Solubility Value Constant.

Andrx's proposed construction of this limitation requires that the wetting agent act to hold the solubility of diltiazem constant. Biovail, on the other hand, seizes upon a statement in the file history to construe this term to mean "not . . . preventing a gradual release of the drug in a uniform manner." Biovail's construction is completely at odds with the usage of the term "maintain" in the specification and other statements in the file history, and denigrates the action of the wetting agent essentially to not standing in the way of releasing diltiazem in a gradual manner. Moreover, Biovail's proposal erroneously conflates "solubility" of a compound with "release" of a compound from a pharmaceutical composition. Finally, Biovail attempts to replace the term "diltiazem", which the parties agree refers to the free-base diltiazem, with the nebulous term "the drug," which might refer to ***either*** free-base diltiazem ***or*** a diltiazem salt.

The specification uses the term "maintain" in its common, ordinary manner. For example, the specification states that during a particular dissolution test, "the temperature was ***maintained*** at 37±0.5°C. (J.A. Tab 1, A-7 at 7:12-13 (emphasis added).) Because the specification uses the term in its customary manner of holding a particular value constant, the use of the same term in the claim should not be given a different meaning.

This usage is also in accordance with dictionary definitions of "maintain." The Webster's Encyclopedic Unabridged Dictionary of the English Language defines maintain as "to keep in existence or continuance, preserve, retain," and "to keep in due condition, operation, or force; keep unimpaired." (J.A. Tab 10, A-104.)

Despite this clear usage in the specification, Biovail relies upon a modified portion of a cherry-picked statement in the file history to generate a definition far beyond the common ordinary meaning. During the prosecution of the '791 patent, the applicants stated that "[t]his control [referring to the activity of the wetting agent] affords a gradual release of diltiazem in a relatively uniform manner over a period of about 24 hours." (J.A. Tab 4, A-51.) Unhappy with even that statement, Biovail eliminates the final clause ("over a period of about 24 hours"), replaces the clear reference to "diltiazem" (which the parties agree refers solely to free-base diltiazem) with the nebulous "the drug," and reformulates the beginning of the quotation as a double negative, such that the wetting agent under Biovail's construction need only "not . . . prevent a gradual release of the drug in a relatively uniform manner."

Biovail's construction is completely at odds with the repeated statements by the applicants during the prosecution of the '791 patent of the importance of the wetting agent in admixture with diltiazem salts to the functioning of the invention. The applicants repeatedly argued the importance of the wetting agent in admixture to the patent office to overcome prior art rejections. (*See, e.g.*, J.A. Tab 4, A-51 – A-52; J.A. Tab 5, A-71 – A-72 ("This [referring to the wetting agent in admixture] is quite important due to the wide variation in pH in the gastrointestinal tract.").) Consequently, Biovail may not now turn their back on the critical wetting agent limitation by now arguing that the claims cover compositions so long as the wetting agent does not prevent gradual release of drug.

c) "Each Bead" Means Every Single Bead.

For the same reasons as described above in Section IV.A.3, above, the term "each bead" in this limitation should be read to mean every single bead in the galenical composition. Claim terms appearing more than once in a claim should be given the same meaning. *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed. Cir. 2001) ("a claim term should be construed consistently with its appearance in other places in the same claim or in other claims of the same patent"); *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335, 1345 (Fed. Cir. 1998) ("the same word appearing in the same claim should be interpreted consistently").

For all of these reasons, Andrx requests that the Court construe the limitation in accordance with Andrx's proposed construction.

7. The Term "Ensuring That The Solubility Of The Diltiazem Is Unaffected By The pH Of The Gastrointestinal Tract Or Other Adverse Conditions Which The Composition Will Meet Therein" Requires That The Wetting Agent Act To Ensure The Solubility Of The Diltiazem Is Unaffected By The pH Of The Gastrointestinal Tract Or Other Adverse Conditions.

Andrx's Construction	Biovail's Construction
This limitation requires that the wetting agent be homogeneously admixed with the diltiazem salt so that the wetting agent will act in the composition to ensure the solubility of diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions the composition would meet if and when the composition is ultimately ingested by a patient. These adverse conditions can include changes in ionic strength, changes in temperature, or changes in pH.	Means the wetting agent does not permit the solubility of the diltiazem to be affected by the pH or other adverse conditions of the gastrointestinal in a manner that would prevent a gradual release of the drug in a relatively uniform manner. The term solubility means the condition of being soluble.

The claim construction issue relating to this limitation is whether the wetting agent must act within the bead to ensure that the diltiazem solubility is unaffected by the

changing pH conditions found in the gastrointestinal tract, which the composition would meet if and when the composition were ultimately ingested. For the same reasons discussed in detail above in connection with the limitation "to maintain the solubility of the diltiazem in each bead," Andrx requests that the Court construe the limitation in accordance with Andrx's proposed construction.

8. The Term "Said Beads Being Coated With A Microporous Membrane" Requires That The Microporous Membrane Be Placed On The Outside Of The Bead.

Andrx's Construction	Biovail's Construction
This limitation refers to the membrane that is to be placed on the outside of each bead which is capable of forming micropores that contains the ingredients referred to later in the claim.	Means that the beads have a microporous membrane.

The claim construction issue as to this limitation is whether the beads are coated with a microporous membrane, or whether the microporous membrane is part of the bead itself, as is the case under Biovail's proposed construction.

a) The Plain Claim Language Makes Clear That The Microporous Membrane Coats The Bead.

Biovail's proposed construction is strange in that it appears that Biovail considers the microporous membrane to be a part of the bead itself. Andrx's construction, instead, considers the microporous membrane as a separate entity layered over the outside of the bead. Andrx's construction better comports with the plain claim language, which requires that the claimed beads be "coated" with a microporous membrane.

b) The Intrinsic Evidence Supports Andrx's Construction.

As discussed above in connection with the claim limitation "beads," the '791 patent specification and file history uniformly describe the bead as the dried product of the spheronization process (such as described in Examples 1 and 2) that is subsequently coated with a microporous membrane. Indeed, the bead cannot be read to include the microporous membrane, because such a construction flies in the face of the '791 patent specification, *e.g.*, the "microporous membrane may be applied ***onto said beads*** by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads." (J.A. Tab 1, A-5 at 4:64-67 (emphasis added).)

Andrx's proposed construction should be adopted because Biovail's proposed construction would exclude embodiments disclosed in the specification.

Similarly, if Biovail's construction were correct, and the bead were defined to include the microporous membrane, then the embodiments described in the '791 patent specification at Examples 3 and 4 would fall outside the scope of the claimed invention because such a coated bead could ***never*** be homogeneous. The membrane (with its water-insoluble polymer) would ***always*** be chemically different from the interior portion of the coated bead. While such a construction would undoubtedly end the matter here in this Court because Biovail could not prove that such a multi-component bead were homogeneous, such a construction would likely violate the well-settled proscription against construing claims in a manner which excludes preferred embodiments disclosed in the specification. *Anchor Wall Sys., Inc. v. Rockwood Retaining Walls, Inc.*, 340 F.3d 1298, 1308 (Fed. Cir. 2003) ("it is axiomatic that a claim construction that excludes a preferred embodiment . . . 'is rarely, if ever correct and would require highly persuasive evidentiary support.'") (quoting *Vitronics,* 90 F.3d at 1583).

B. THE CLAIMS OF THE '866 PATENT[5] SHOULD BE CONSTRUED BASED ON THE INDUSTRY STANDARD TEST METHODS THAT EXPRESSLY ARE INCORPORATED BY REFERENCE IN THE CLAIMS AND RECITED IN THE SPECIFICATION.

The '866 patent primarily concerns the observed dissolution and pharmacokinetic properties of a diltiazem composition. Specifically, the claims of the '866 patent require that the diltiazem of the composition either dissolves at a particular rate in water, or dissolves at different particular rate in a buffered solution. Industry standard methods for testing dissolution of active ingredients in tablets or capsules at the time is found in Section <711> of the United States Pharmacopeia ("USP") No. 23.

With respect to pharmacokinetics, the claims require that the compound exhibit a higher "bioavailability" when administered at night than during the day. They also call for the compound to be "bioequivalent" when administered in the morning with or without food. The terms "bioavailability" and "bioequivalence" are terms of art, defined and applied by the Food and Drug Administration ("FDA"), in test protocols and criteria published in official agency technical guidance.

Andrx proposes to construe the dissolution and pharmacokinetic claim language in accordance with the USP and FDA standards and criteria either directly incorporated or incorporated by reference in the specification. Biovail essentially declines to provide any meaningful definition for the dissolution testing claim limitations. That is, Biovail seeks to avoid any construction against which the strength (or weakness) of its infringement evidence can be readily assessed. For the pharmacokinetic claim terms, Biovail simply ignores the incorporated FDA guidance, and proposes its own novel criteria for comparing bioavailability and bioequivalence.

[5] All disputed claim terms in the '866 patent are found in claim 1.

1. The Court Should Construe The Claimed Dissolution Results "Measured Using The Methods Of USP No. XXIII" To Mean Dissolution Results Obtained Using Apparatus 1 In Accordance With The Procedure And Interpretation Rules Specified In Section <711> of USP No. 23.

Andrx's Construction	Biovail's Construction
The dissolution testing is conducted according to USP 23, p. 1791 [which is Section <711>] using Apparatus 1 (basket), employing the recited acceptance table, i.e. the mean average % releases of a minimum of six vessels.	Dissolution testing is conducted according to the methodology set forth in USP 23.

All asserted claims of the '866 patent include a limitation that the composition release diltiazem at a particular rate in water, or, in the alternative, at a particular rate in a buffered solution. The release or dissolution rates in either the water or buffered solution are to be "measured using the method of United States Pharmacopeia No. XXIII." For instance, Claim 1 requires that the composition:

> (i) releases the diltiazem or a pharmaceutically acceptable salt thereof into an aqueous medium at the following rates ***when measured using the method of United States Pharmacopeia No. XXIII at 100 rpm in 900 ml of water***.
>
> (a) between about 1% and about 15% after about 2 hours;
>
> (b) between about 7% and about 35% after about 4 hours;
>
> (c) between about 30% and about 58% after about 8 hours;
>
> (d) between about 55% and about 80% after about 14 hours;
>
> (e) in excess of about 75% after about 24 hours; and/or
>
> (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates ***measured using the method of United States Pharmacopeia No XXIII at 100 rpm in 900 ml of the buffered medium***:

> (a) between about 1% and about 25% after about 2 hours;
>
> (b) between about 7% and about 45% after about 4 hours;
>
> (c) between about 30% and about 68% after about 8 hours;
>
> (d) in excess of about 75% after about 24 hours.

(J.A. Tab 12, A-137 at 23:46-24:7 (emphasis added).)

The inventors made clear in the specification of the '866 patent that they were defining their invention in terms of dissolution results obtained from using the test protocol in Section <711> of the USP 23, and in particular the use of testing "Apparatus 1" (as opposed to "Apparatus 2") within Section <711>. The inventors stated:

> ***Thus a 24-hour diltiazem preparation is provided*** wherein the Cmax of diltiazem in the blood is provided from about 10-15 hours after administration of a single dosage to a patient about 9-15 hours after multiple dosages over a number of days ***and displays the dissolution described above determined according to USP 23, page 1791 using Apparatus 1.***

(J.A. Tab 12, A-131 at 12:43-49 (emphasis added).) The dissolution standard at page 1791 of USP 23 is entitled "Dissolution" and is denoted as section <711>. (J.A. Tab 20 A-799.) The inventors went on to incorporate into the specification the text of the "Apparatus 1" description from section <711> of USP 23. (J.A. Tab 12, A-131 – A-132 at 12:49-13:19.)[6] Similarly, during the prosecution of the '866 patent, the applicants distinguished dissolution testing according to USP 21 as "not in accordance with Applicant's claimed procedure." (J.A. Tab 13, A-172.)

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[6] In Section <711> USP 23, "Apparatus 1" generally consists of a small basket into which the dosage form is inserted, and is then submerged into the solution in a vessel, and then rotated for the desired time period(s). After being submersed in the rotating basket for the requisite time(s), samples of the solutions are taken and analyzed to determine the percentage of the active ingredient that has dissolved. "Apparatus 2" generally consists of a similar vessel, into which the dosage is introduced, and into which a paddle formed from a blade and shaft is used as the stirring element. (J.A. Tab 20 A-799 – A-800.)

In light of this intrinsic evidence, Andrx maintains that the term "measured using the method of United States Pharmacopeia No. XXIII" should be construed to mean measured in accordance with the procedures and criteria in Section <711> of USP 23, using Apparatus 1.

Biovail, however, insists that the procedures and criteria to be applied can be found somewhere in the USP 23, but refuses to say which section or which apparatus. Joint Claim Chart, Ex. B at 6. That construction is simply indefinite. *See Rhodia Chimie v. PPG Indus. Inc.*, 402 F.3d 1371, 1377-80 (Fed. Cir. 2005) (affirming claim construction that incorporated particular testing methodology to avoid indefinite claim). In effect, Biovail is refusing to say what its own claim term means by insisting that it *might* mean any one or combination of multiple test methods, criteria and apparatuses. In alleged support of its position, Biovail cites to unspecified supplements to the USP, an entirely different test protocol section of the USP (Section <724>), and several USP monographs for diltiazem hydrochloride and products – all without any explanation as to how these actually support their positions. *Id.*

The only intrinsic evidence cited by Biovail does not support Biovail's proposed indefinite construction, and does not render the intrinsic evidence ambiguous. See, Column 5:28-61 of the specification does not identify or refer to any particular page or section of the USP 23, and does not mention any particular apparatus to be used. (J.A. Tab 12, A-128 at 5:28-61.) Biovail simply ignores column 12:42-13:17 of the specification, where the inventors not only defined the invention as having "the dissolution pattern described above determined according to USP 23, page 1791 [Section<711>] using Apparatus 1," but actually reproduced the entire description of Apparatus 1 from Section <711>. (J.A. Tab 12, A-131 – A-132 at 12:42-13:17.)

Apart from Section <711>, which is expressly incorporated in the specification, other sections and portions of the USP 23 cited by Biovail are extrinsic evidence. For instance, there is no reference to section <724> in the specification and Biovail did not

identify any part of the prosecution history that refers to the section. Similarly, Biovail fails to cite any part of the specification or prosecution history in which the inventors referred to or relied on any USP supplements or monographs cited by Biovail.

But even if the USP monograph for diltiazem hydrochloride tablets were admissible, it still would not support Biovail's indefinite construction as to testing apparatus, because the inventors made clear in the specification which apparatus was used to generate the data defining the bounds of their invention. It becomes apparent Biovail's reliance on the USP monograph for diltiazem hydrochloride tablets is a red herring, when considered in the context of the USP.

Outside the world of the '866 patent, the purpose of the testing protocol in Section <711> of the USP is to provide a testing methodology to allow people to determine if tablets or capsules meet the dissolution standards that appear in the USP monograph for that particular tablet or capsule. (J.A. Tab 20 A-799.) Accordingly, for the purposes of determining compliance with data in the monograph, Section <711> indicates that the apparatus specified in the relevant monograph should be used. The USP dissolution data in the monograph for diltiazem hydrochloride tablets reflects USP's prior usage of Apparatus 2. (J.A. Tab 20 A-797.) Thus, if one were using Section <711> for the purpose of determining whether a given diltiazem hydrochloride tablet complied with the dissolution requirements in the USP monograph, one would use Apparatus 2 in order to be able to compare apples to apples (*i.e.*, test data using Apparatus 2 to monograph data obtained by the USP using Apparatus 2), rather than apples to oranges (*i.e.*, test data using Apparatus 1 to monograph data obtained by the USP using Apparatus 2).

Inside the world of the '866 patent, however, the inventors' explicit and consistent use of Apparatus 1 to describe their invention in the specification unambiguously puts the person of ordinary skill on notice that the bounds of their invention are to be defined using the same apparatus. In much the same way that the USP announced Apparatus 2 for determining whether a tablet complies with the dissolution requirement in the USP

monograph product, the inventors announced Apparatus 1 for determining whether an accused dosage form meets the dissolution limitations for the '866 patent. The purpose and utility of both announcements was similar – to ensure a comparison of apples to apples (*i.e.*, dissolution data from Apparatus 1 vs. dissolution data in the '866 patent obtained by Apparatus 1), rather than apples to oranges (*i.e.*, dissolution data from Apparatus 2 vs. dissolution data in the '866 patent obtained by Apparatus 1).

Finally, Biovail rejects any claim construction that incorporates the rules for interpretation and acceptance of results within Section <711> of USP 23. These rules obviously are an integral part of the testing procedure because they reflect the USP's judgment of when and under what circumstances data generated by its own testing protocol are meaningful. And for results to be meaningful, the USP has made clear that dissolution results must be obtained from a minimum of six (6) samples in vessels. Biovail rejects Andrx's position, but refuses to provide any meaningful alternative. Biovail is refusing to say what its own claim term means by insisting that it *might* require any number of units to be tested, and then refusing to say how many units. Joint Claim Chart, Ex. B at 6.

Andrx's intrinsic evidence comes from Section <711> of the USP 23, expressly incorporated by reference in the specification. The part of Section <711> entitled "Interpretation" instructs the user that a dissolution requirement for "Q" percentage of an active ingredient dissolved at a given time point is deemed "met" if the amount of active ingredient dissolved conform to the following acceptance table, in which S1, S2 and S3 represent three stages of testing, and Q is defined as the desired quantity of the active ingredient dissolved, expressed as a percentage if the labeled content of the product.

Stage	Number Tested	Acceptance Criteria
S1	6	Each unit is not less than Q+5%
S2	6	Average of 12 units (S1 + S2) is equal to or greater than Q, and no unit is less than Q-15%.
S3	12	Average of 24 units (S1 + S2 + S3) is equal to or greater than Q, not more than 2 units are less than Q-15%, and no unit is less than Q-25%.

(J.A. Tab 20 A-801.) The USP explains that if the specimen fails to meet the dissolution requirement "Q" in stage 1 (S1) testing, the user should then proceed with stage 2 and 3 (S2 and S3) testing. *Id.*[7] This USP table from Section <711> makes clear that the absolute minimum number of units necessary in order to generate sufficiently reliable data for acceptance is six (6) units.

Andrx requests the Court to adopt a construction of "measured using the method of United States Pharmacopeia No. XXIII" that (a) requires the testing procedures of Section <711> of the USP, with Apparatus 1, and (b) requires the use of interpretation and acceptance criteria of Section <711> of the USP, which in turn requires a minimum of six (6) units to be tested.

[7] Thus, for example, if the dissolution requirement of a given monograph was that 50% of the active ingredient dissolve in two hours, the specimens meet that requirement if each of 6 units tested had a dissolution of 55%. If any of the 6 units tested did not reach this requirement, the product could still meet the 50% requirement if another 6 units were tested, and the average of the first 6 and second 6 units tested was equal to or greater than 50%, with none of the 12 units being less than 35% dissolved. And if the 12 samples failed to meet the S2 criteria, the product still might be deemed by the USP to meet the requirement under S3 criteria, if another 12 units were tested (for a total of 24), and the average of all units was equal to or greater than 50%, and not more than 2 units were less than 35%, and no units were less than 25%.

2. The Claim Term "Higher Bioavailability When Given At Night Compared To When Given In The Morning Without Food According To FDA Guidelines or Criteria" Should Be Construed To Mean Bioavailability A Defined And Measured By The FDA In FDA Guidelines And Criteria Expressly Incorporated In The Specification Of The '866 Patent.

Andrx's Construction	Biovail's Construction
Means a formulation when administered at night under appropriate test parameters exhibits a log transformed mean AUC and C_{max} that exceed the log-transformed 90% confidence interval for the same formulation when administered in the morning without food, as determined in accordance with FDA guidance documents incorporated in the specification.	Means the composition gives a night vs. day dosing ratio of >1 for AUC and Cmax when giving without food.

All asserted claims of the '866 patent include a limitation that the composition exhibit a higher "bioavailability" when given at night instead of during the day to be determined "according to FDA guidelines or criteria." Claim 1, for example, requires that the composition exhibit "a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria." (J.A. Tab 12, A-137 at 24:13-18.)

The inventors expressly identified the FDA guidelines in the specification:

> The FDA guidelines are those entitled:
>
> "GUIDANCE ORAL EXTENDED (CONTROLLED) RELEASE DOSAGE FORMS IN VIVO BIOEQUIVALENCE AND IN VITRO DISSOLUTION TESTING" prepared under 21 CFR 10.90(b)(9) by Shrikant V. Dighe, Ph.D., Director, Division of Bioequivalence Office of Generic Drugs dated Sep. 3, 1993 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs, Center for Drug Development Research dated Sep. 4, 1993, which is incorporated herein by reference; and
>
> "GUIDANCE STATISTICAL PROCEDURES FOR BIOEQUIVALENCE STUDIES USING A STANDARD TWO-TREATMENT CROSSOVER

> DESIGN" prepared under 21 CFR 10.90(b) by Mei-Ling Chem, Ph.D., Division of Bioequivalence Review Branch II dated June 12, 1992 and Rabindra Patnaik, Ph.D., Division of Bioequivalence Review Branch II dated June 26, 1992, approved by Shirkant V. Dighe, Ph.D., Director, Division of Bioequivalence dated June 29, 1992 and concurred by Roger L. Williams, M.D., Director, Office of Generic Drugs dated June 29, 1992, which is incorporated herein by reference.

(J.A. Tab 12, A-129 at 8:13-34.) The inventors went on to quote at considerable length portions of this FDA guidance. (J.A. Tab 12, A-129 at 8:35-12:12.)

The parties agree that "bioavailability" is a combination of pharmacokinetic parameters "AUC" and "C_{max}," which reflect the total amount of drug released and the peak concentration of drug in plasma after administration to a human. The parties disagree as to (a) the protocol to be followed in obtaining AUC and C_{max} data, and (b) the criteria by which the AUC and C_{max} for nighttime administration meaningfully can be said to be higher than the calculated bioavailability for daytime administration – *i.e.*, the statistical significance of any differences.

Andrx maintains that the AUC and C_{max} data to be compared should come from the pharmacokinetic test protocols in the FDA guidance documents expressly incorporated into the specification of the '866 patent. Biovail declines to take any position as to the protocol to be used to generate the AUC and C_{max} data to be compared. Joint Claim Chart, Ex. B at 8. Again, Biovail essentially refuses to say what its own claim means by insisting that it *might* mean data generated by any number of unspecified test protocols.

With respect to statistical significance, Andrx construes the "higher bioavailability" of nighttime administration to mean that the log-transformed mean AUC and C_{max} measurements for nighttime administration in tests conducted according to the FDA guidance are greater than the 90% confidence interval for the log-transformed AUC and C_{max} measurements for daytime administration conducted under the same protocol –

i.e., a comparison between the observed log-transformed mean AUC and C_{max} and what is calculated to be the log-transformed mean AUC and C_{max} (with 90% statistical confidence) for daytime administration.

Andrx's proposed 90% confidence interval comes directly from the FDA guidance for comparing pharmacokinetic data, which the inventors incorporated by reference and chose partially to reproduce in the specification. (J.A. Tab 12, A-129 at 8:13-12:13.) These statistical guidelines expressly call for the use of a 90% confidence interval in comparing the log mean AUC and C_{max} of a test product and reference product. (J.A. Tab 12, A-129 at 8:46-47, 8:56-57; J.A. Tab 18, A-757 and A-759; *see also* J.A. Tab 19, A-768 and A-773.) Applied to the "higher bioavailability" for nighttime administration in the patent claims, the AUC and C_{max} for nighttime administration would be the test product, and the AUC and C_{max} for daytime administration would be the reference product.

Biovail rejects Andrx's construction, and proposes its own statistical criterion for comparison instead of that 90% confidence interval used in the specification. Biovail proposes to construe the term "higher bioavailability" to mean any product for which the mean AUC and C_{max} for nighttime administration is greater (by any amount, regardless of statistical significance) than the mean AUC and C_{max} for daytime administration. Biovail expresses this as any value greater than one (1) for a ratio of AUC and C_{max} for nighttime to daytime administration. Joint Claim Chart, Ex. B at 8.

Biovail cites several portions of the specification, but none support its position. For instance, Biovail cites the incorporation and lengthy quotation of the FDA guidance documents upon which Andrx relies, but Biovail fails to explain how any of these documents support a comparison of bioavailability without the 90% confidence interval that they so plainly require. Joint Claim Chart, Ex. B at 8 (citing '866 Patent Specification (J.A. Tab 12, A-129 and A-132) at 8:6-12:24 and 14:10-16). Biovail's other cited portion of the specification also refers to the FDA guidelines, and identifies

25% more bioavailability as an example of "higher bioavailability" within the meaning of the invention. *Id.* (citing '866 Patent Specification (J.A. Tab 12, A-131) at 12:33-41). It is not clear why Biovail cites this section, especially in light of the fact that Biovail is not advocating 25% higher bioavailability as the meaning of "higher bioavailability."

Biovail's only arguable support comes from the prosecution history, in two responses filed with the PTO, in which Biovail argued that an embodiment of the claimed invention (a Biovail product called "Cardizem LA") exhibited higher bioavailability because both AUC and C_{max} were greater than 1. (*See, e.g.,* J.A. Tab 16, A-481 – A-484); Tab 17, A-658 – A-661 and A-663 – A-667.) It is undisputed that the arguments presented in these submissions did not result in allowance, but rather failed to overcome the PTO's anticipation and obviousness rejections. But more importantly, as a matter of law, the fundamental problem with Biovail's reliance on this prosecution history is that the specification, upon which Andrx relies, "is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed.Cir. 1996); *Boss Control, Inc. v Bombardier, Inc.*, 410 F.3d 1372, 1377 (Fed. Cir. 2005).

For these reasons, the Court should construe "a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria" to mean the comparative testing protocols for AUC and C_{max} in the FDA guidelines incorporated by reference and quoted in the specification.

3. The Claim Term "Bioequivalence When Given In The Morning With Or Without Food According To The Same FDA Guidelines Or Criteria" Should Be Construed In Accordance With The Same FDA Guidelines That Define "High Bioavailability."

Andrx's Construction	Biovail's Construction
Means a formulation when given in the morning with food under appropriate test parameters that exhibits a log mean AUC and C_{max} within the 90% confidence	Means food does not render the composition bioinequivalent when the composition is given in the morning with or without food.

interval for the log mean AUC and C_{max} of the same formulation administered without food if the first was with food, and with food if the first was without food, in accordance with FDA guidance documents incorporated in the specification.	

The last disputed claim term of the '866 patent is the limitation in every asserted claim that the composition exhibit "bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria." (*See, e.g.,* J.A. Tab 12, A-137 at 24:16-18.) It is undisputed that the "same FDA guidelines" refers to the FDA guidelines previously discussed in connection with the term "higher bioavailability," above.

Accordingly, Andrx adopts the same construction based on the specification, which calls for specific test protocols and applies the 90% confidence interval for comparison of AUC and C_{max} of a test sample (the fed sample) and the reference (the fasted sample). (J.A. Tab 12, A-129 at 8:46-47, 8:56-57; J.A. Tab 18, A-757 and A-759; *see also* J.A. Tab 19, A-768 and A-773.)

Biovail essentially refuses to proffer a construction, insisting that the meaning of "bioequivalence" is not causing something to be "bioinequivalent" – a circular definition that includes a made-up word, "bioinequivalent." Joint Claim Chart, Ex. B at 10. None of the specification passages cited by Biovail, however, identifies any other test protocol or method of comparing AUC and C_{max} for fed vs. fasting morning administration.

For the same reasons, therefore, the Court should construe "bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria" to require testing protocol according to the FDA guidance, and AUC and C_{max} results for fed morning administration to be within the mean for AUC and C_{max} results for fasted morning administration.

V. CONCLUSION

For the foregoing reasons, Andrx respectfully requests that the Court construe the disputed limitations in accordance with Andrx's proposed constructions.

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Dated: March 30, 2007

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Kenneth L. Dorsney, hereby certify that on March 30, 2007, the attached document was hand-delivered on the following persons and was electronically filed with the Clerk of the Court using CM/ECF which will send notification of such filing(s) to the following and the document is available for viewing and downloading from CM/ECF.

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